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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,593	12/05/2001	Katherine S. Bowdish	1087-2	3532

7590 10/18/2005

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EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,593	BOWDISH ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08.15.2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,36,44,45,85-92 and 96-99* is/are pending in the application.

4a) Of the above claim(s) *17,20,21,91 and 92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18,19,22,23,36,44,45, 85-90 and 96-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07.19.2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 08/15/2005, and a response to the arguments is set forth.

2. Claims 17, 20-21, 91-92 are withdrawn from further consideration pursuant to 37CFR 1.142(b), as being drawn to nonelected inventions.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior office action.

4. Claims 44, 86 and 99 have been amended.

5. Claims 1-16, 18-19, 22-23, 36, 44-45, 85-90 and 96-99 are under examination.

Rejections withdrawn

5. The rejection of claims 44-45, 85-89 and 99 under 35 U.S.C. 112, second paragraph is withdrawn in view of the amendments to the claims.

Response to Arguments

6. The rejection of claims 1-16, 18-18, 22-23, 36, 44-45, 85-90 and 96-99 under 35 U.S.C. 103(a) as obvious in light of Barbas et al (a) (WO 94/18221, published 8/94) and further in view of Dower et al (WO 96/40750, published 12/96) and Barbas et al (b) (PNAS 92:2529-2533, 1995) and as evidenced by Helms et al (Protein Science 4:2073- 2081, 1995) is maintained.

The applicant argues that "Barbas PCT is a generic disclosure of incoporating a binding site" into a CDR. This generic disclosure provides no

motivation or suggestion whatsoever that it is desirable, practical, or even possible to incorporate the specifically recited EPO and TPO mimetics into the immunological molecule or fragment(s) thereof and that the Barbas PCT application fails to disclose incorporation of a TPO or EPO mimetic into an immunoglobulin molecule as recited by claim 1 (page 10, 2nd paragraph). The Applicant further argues that the antibodies of the current invention are distinguishable from that of Barbas PCT in that they have agnostic properties (page 11, 2nd paragraph). The Applicant further argues that "the proposed modification of adding the mimetics of Dower to the immunoglobulin of Barbas PCT would likely render Dower unsatisfactory for the intended purpose of making defined low molecular weight peptides and peptide mimetics having strong binding properties to he TPO-R, and further that Dower teaches away from using the larger molecular weight proteins of Barbas PCT" (page 12, 2nd paragraph). The applicant further argues that the Barbas Publication fails to cure the deficiencies of Barbas PCT and that nowhere does the Barbas publication teach or suggest that it is desirable, practical or even possible to incorporate the specifically recited EPO or TPO mimetics into an immunoglobulin molecule or fragment thereof and thus, one would not be motivated to combine this reference teaching invention which requires an EPO or TPO mimetics, to arrive at the claimed invention which requires an EPO or TPO mimetic (pages 12 and 13 bridging paragraph). The applicant also argues that there is no suggestion of motivation to substitute the sequences grafted onto the heavy chain of an anti-tetanus toxoid Fab or Barbas (b) with the EPO and TPO mimetics, and

incorporate the mimetics into the proteins of Barbas PCT, and claim 1 is not obvious. The Applicant further argues that Kini adds prolines to the end of very short peptides to give them a definitive secondary structure, but such should not be needed when the peptide is placed in the middle of a large protein (pages 13 and 14, bridging paragraph). The argument further states that none of the applied references teaches or discloses that the presence of a proline at the carboxy terminus of the inserted biologically active peptide is particularly useful compared to any other amino acid at that position (page 15 lines 5-10). In addition, the applicant argues that "it has been surprisingly found by Applicants that a proline flanking the peptide can provide an increase in biological activity of the inserted biologically active peptide" and that there is no motivation or suggestion in the Kini reference to insert a biologically active peptide flanked with a proline at the carboxy terminus into or in place of an antibody CDR (page 16 lines 9-13).

The applicant thus seems to be arguing the rejections by commenting on the cited references individually. In response to applicants arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to the applicants arguments, the examiner states the following: Under 35 U.S.C. 103 it is only necessary to establish motivation to combine the references, and that the ordinary skilled artisan would have

reasonable expectation of success being able to produce the invention. Applicant's arguments are not found persuasive that, assuming unpredictability in combining the cited references to produce an immunoglobulin molecule or fragment thereof comprising a region where amino aid residues corresponding to at least a portion of a CDR are replaced with a peptide mimetic selected from the group consisting of EPO mimetics and TPO mimetics, wherein the immunoglobulin molecule or fragment thereof binds an EPO or TPO receptor, one of ordinary skill would not be motivated and would not reasonably expect to be successful. As stated in the previous office action, methods of replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking sequences for presenting a biological peptide in a conformation for binding to a receptor were well established in the art at the time the invention was made, and the biologically active peptides (EPO mimetics and TPO mimetics) identical to the claimed invention were also known. Thus, the two critical elements required to make the instant invention were known in the art at the time the invention was made. Further, the argument that "adding the mimetics of Dower to the immunoglobulin of Barbas PCT would likely render Dower unsatisfactory and that Dower teaches away from using the larger molecular weight proteins of Barbas PCT" is not persuasive because no where in the reference does Dower teach away from using large molecular weight proteins. In addition, Dower et al teach that the molecular weight of the peptide mimetic can be from about 250 to about 8000 daltons (paragraph 13), which is considerably large in comparison to the lengths

of a CDR. In response to the argument that the antibodies of the current invention are distinguishable from that of Barbas PCT in that they have agnostic properties, the examiner states that the property of an antibody is irrelevant when the methods of making an antibody, the CDR comprising the antibody and motivation for the addition of residues to the CDR peptides for a better presentation of recognition sites is well known in the art. Further, the applicants argument that Barbas Publication fails to cure the deficiencies of Barbas PCT in that nowhere does the Barbas publication teach or suggest that it is desirable, practical or even possible to incorporate the specifically recited EPO or TPO mimetics into an immunoglobulin molecule is not found persuasive for the reasons as set forth: Barbas PCT teaches methods of replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and Barbas publication teaches replacement of CDR3 in the anti-tetanus toxoid antibody with several sequences. Thus, combining these references with the teachings of Dower et al (as describe above), it would have been obvious to replace the peptide for a CDR in the heavy or light chain of an antibody because Barbas PCT teaches that human antibodies have benefits of therapy in vivo in humans for blocking or inhibiting the target and because Barbas publication teaches replacement in the anti-tetanus antibody of unrelated sequences from that in the CDR and the antibody binds the target; and since antibody tertiary structures are homologous one skill in the art would conclude that the anti-tetanus antibody could be used for other sequences to present and in view of Dower et al who teach that the TPO peptides can be used for therapy, one would

have motivation to add the peptide to the antibody CDR. The applicants argument that Kini adds prolines to the ends of very short peptides to give them a definite secondary structure, but such should not be needed when the peptide is placed in the middle of a large protein is not persuasive because Kini et al teach the incorporation of proline brackets within the peptide sequences, in addition that proline brackets introduce no undue strain along the backbones, and thus allow flexibility of the interaction sites (page 16 column 2, in particular). In response to the applicants arguments that there is no motivation or suggestion in the Kini reference to insert a biologically active peptide flanked with a proline in place of an antibody CDR, the applicant is again reminded that because Barbas PCT teaches methods of replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptide, and since Kini et al teach a novel approach to the design of potent bioactive peptides by incorporation of proline brackets (title in particular) and that proline residues help in the presentation of interaction sites and that it is logical to propose that the incorporation of proline residues around a bioactive peptide might enhance its potency significantly (see introduction on page 15) and as evidenced by the specification that the EPO and TPO mimetics are biologically active peptides, it would have been obvious and one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the biologically active peptides as modified, via incorporation of proline residues, by the teachings of Kini et al to in place of CDRs within a heavy or light chain as taught by Barbas PCT. Furthermore, since the claimed EPO and TPO peptide mimetics are taught by

Dower et al it would have been obvious to one of ordinary skill in the art to combine the teachings of Barbas PCT, Kini et al and Dower et al to produce the claimed immunoglobulin molecule.

The applicant further argues that "a proline flanking the peptide can provide an increase in biological activity of the inserted biologically active peptide, and that is these various proline-extended embodiments that are embraced by claims 19, 44, 45 85, 87-89 and 96" (page 15 lines 10-11). However, the claims consist of a number of flanking amino acid sequences that do not consist of the amino acid proline. For this reason, the claim and the argument is not commensurate with the scope and hence the rejection as stated in the previous office action is maintained and the argument is not found persuasive.

In response to applicants arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the teachings of Barbas PCT in replacing CDRS in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking sequences for presenting a biological active peptide in a conformation for binding to a receptor for and the teachings of Dower et al indicating the

peptide sequences of TPO that bind the thrombopoietin receptor and SEQ ID NO:2 without the proline at the C-terminus (which is SEQ ID NO:1, see page 26-30 and Table 7 and 9 and specifically page 76, top molecule which comprises SEQ ID NO:1 with cysteines flanking the sequence, and claim 19 which claims the sequence of SEQ ID NO:1 (see last compound) and the addition of flanking sequences for structural constraints (see page 45, lines 10-14) and the teachings of Barbas Publication teach replacement of CDR3 in the anti-tetanus toxoid antibody with several sequences and the teachings of Kini et al indicating the design of biologically active peptides with proline residues flanking the sequence and the prolines resulted in restricting the conformation and in enhanced activity of the peptides would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

Conclusion

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is ~~703-872-9306.~~ 571-273-8300

10. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi Ph.D.
(571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER